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(54) **Acylbiphenylylaminoalkanoic acids**

(57) Acylbiphenylylaminoalkanoic acids of the general formula I

$$R^1-CO-N(A)-C_nH_{2n}-COOH \qquad (I),$$

in which R^1 signifies an aliphatic or alicyclic hydrocarbon radical or an optionally substituted phenyl group, A signifies an optionally substituted and/or hydrogenated biphenylyl radical and n signifies a positive whole number from 3 to 5, as well as their salts of inorganic or organic bases exert on warm-blooded animals a protective action on the stomach and liver, and in addition they bring about an increase in the secretion of the pancreas and liver. In addition, they cause an inhibition of the formation of glucose from lactate and pyruvate in the liver. They are suitable for the treatment and prophylaxis of diseases which are due to disorders of the stomach or intestine or to reduced performances by the pancras, bile and/or liver. Processes for the production of the compounds and corresponding pharamaceutical products are given.

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SPECIFICATION

Substituted amino acids, their use and production and pharmaceutical products containing same

The Invention relates to substituted amino acids, their use and production and pharmaceutical products containing them.

The compounds according to the invention are used in the pharmaceutical industry for the preparation of medicaments.

In the investigation of N - benzoyl - anilinoalkanecarboxylic acids (D. Evans et al., J. Med. Chem. 12 (1969) 1006-10) the corresponding butyric acids showed no action of inhibiting inflammation, whilst in German published unexamined Patent Application DE-OS 19 17 036 N - acyl - anilinoalkanoic acids with a choleretic action are described, to which there are also ascribed further effects (DE-OS 2 450 680). α - Phenyl - benzylidene - ω - amino - alkanoic acids and their derivatives are said to be used in agents with an anti-epileptic action (DE-OS 2 634 288). In further German published unexamined Patent Applications (DE-OS 2 131 626, 2 131 674, 2 131 675, 2 131 679 and 2 131 680) trialkoxy - benzoyl - aminoalkanecarboxylic acids are described which may be used for the prophylaxis and treatment of the cardiac infarction. Now a new class of acylbiphenylylaminoalkanoic acids has been synthesised which are not mentioned in the publications cited nor are they rendered obvious by them. Furthermore it has been found that these acylbiphenylylaminoalkanoic acids possess interesting and particularly advantageous pharmacological properties.

The Invention relates to acylbiphenylylaminoalkanoic acids of the general formula I

$$R^1-CO-N(A)-C_nH_{2n}-COOH \qquad (I),$$

in which

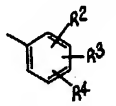
R^1 signifies an aliphatic or alicyclic hydrocarbon radical or an optionally substituted phenyl group,

A signifies an optionally substituted and/or hydrogenated biphenylyl radical,

n signifies a positive whole number from 3 to 5, and their salts of inorganic or organic bases.

As aliphatic hydrocarbon radicals which may be saturated or unsaturated, one may use straight or branched alkyl radicals with 1 to 7 carbon atoms. Straight alkyl radicals are the methyl, ethyl, propyl, butyl, pentyl, hexyl or heptyl radical, of which those with 1 to 5, particularly 1 to 3, carbon atoms are preferred. Branched alkyl radicals with 3 to 7 carbon atoms are, for example, the isopropyl, isobutyl, sec.-butyl or tert.-butyl radical, of which those with 3 to 5, particularly with 3 carbon atoms are preferred. Unsaturated hydrocarbon radicals are alkenyl and alkinyl radicals with 2 to 7 carbon atoms, for exanple the ethenyl, the ethinyl, the 1-propenyl, 1,3-butadienyl, 2-butinyl radical, of which the 1-propenyl radical is preferred. As alicyclic hydrocarbon radicals one may use cycloalkyl radicals with 3 to 10 carbon atoms, for example the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl radical, of which those with 5 to 7 carbon atoms are preferred.

As optionally substituted phenyl groups one may use those of the formula



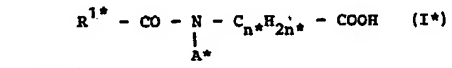
in which R^2, R^3 and R^4 are the same or different and signify a hydrogen atom, a halogen atom, an alkyl group, a hydroxy group, an alkoxy group, an acyloxy group, an optionally substituted amino group, a nitro group or a trifluoromethyl group. As halogen atoms R^2, R^3 and R^4 one may use fluorine, chlorine or bromine, preferably fluorine and chlorine, especially chlorine. As alkyl groups or alkoxy groups R^2, R^3 and R^4 one may mention inter alia those with 1 to 4 carbon atoms, of which those with 1 to 3, particularly those with 1 carbon atom are preferred. As acyloxy groups one may consider inter alia –O–CO–R^1 groups, in which R^1 has the meaning given above, of which the alkanoyloxy group with 1 to 7, especially 2 to 5 carbon atoms, particularly the acetoxy group, are preferred. Besides the unsubstituted amino group one may use as substituents R^2, R^3 and R^4 preponderantly substituted amino groups, of which for example one may mention alkylamino and dialkylamino groups with 1 to 4, preferably 1 or 2, carbon atoms in the alkyl radical, as well as acylamino groups with the usual acyl groups used for protecting amino groups, such as alkanoyl groups with 2 to 5 carbon atoms.

As biphenylyl radicals one may use the 2-, 3- or 4-biphenylyl radical. Partially hydrogenated biphenylyl radicals are for example the 4 - cyclohexyl - phenyl radical, the 4-phenylcyclohexyl radical, the 2-cyclohexylphenyl radical. As substituents one may use halogen atoms, for example fluorine, chlorine or bromine, preferably chlorine, alkyl or alkoxy groups with 1 to 4, preferably 1, carbon atoms, optionally substituted amino groups, hydroxy or nitro groups.

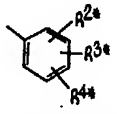
As salts one may use salts of inorganic and organic bases. Pharmacologically incompatible salts are converted by known methods into pharmacologically, that is to say biologically, compatible salts, which are preferred among the salts according to the Invention. As cations for the salt formation one uses mainly the cations of the alkali metals, alkaline earth metals or earth metals, but it is also possible to use the corresponding cations of organic nitrogen bases, such as amines, aminoalkanols, amino sugars or basic amino acids.

For example one may mention the salts of lithium, sodium, potassium, magnesium, calcium, aluminium, ethylenediamine, dimethylamine, diethylamine, morpholine, piperidine, piperazine, methylcyclohexylamine, benzylamine, ethanolamine, diethanolamine, triethanolamine, tris - (hydroxymethyl) - amino - methane, 2 - amino - 2 - methyl - propanol, 2 - amino - 2 - methyl - 1, 3 - propandiol, glucamine, N-methylglucamine, glucosamine, N-methylglucosamine, lysine, ornithine, arginine, quinoline.

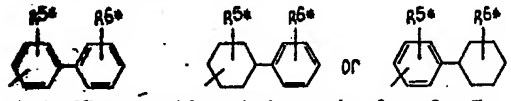
A modification of the Invention consists of acylbiphenylylaminoalkanoic acids of the general formual I*



in which
R^{1*} signifies an aliphatic hydrocarbon radical with 1 to 7 carbon atoms, an alicyclic hydrocarbon radical with 3 to 10 carbon atoms or a phenyl radical

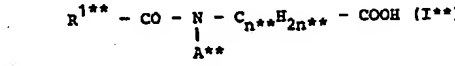


A* signifies a group of the formula

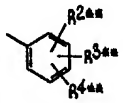


n* signifies a positive whole number from 3 to 5,
R^{2*}, R^{3*} and R^{4*} are the same or different and signify a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group with 1 to 4 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkanoyloxy group with 2 to 5 carbon atoms, a nitro group or a trifluoromethyl group,
R^{5*} and R^{6*} are the same or different and signify a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a hydroxy group or a nitro group,
and their salts of inorganic or organic bases.

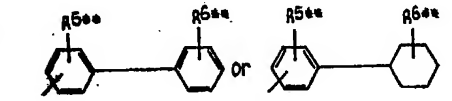
Another modification of the Invention consists of acylbiphenylylaminoalkanoic acids of the general formula I**



in which
R^{1**} signifies an aliphatic hydrocarbon radical with 1 to 5 carbon atoms, an alicyclic hydrocarbon radical with 5 to 7 carbon atoms or a phenyl radical

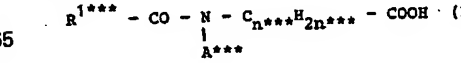


A** signifies a group of the formula

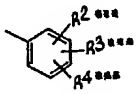


n* signifies a positive whole number from 3 to 5,
R^{2**} signifies a hydrogen atom,
R^{3**} and R^{4**} are the same or different and signify a hydrogen atom, a halogen atom, a hydroxy group, a methoxy group, a methyl group, an alkanoyloxy group with 2 to 5 carbon atoms, a nitro group or a trifluoromethyl group,
one of the substituents R^{5**} or R^{6**} signifies a hydrogen atom and the other signifies a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a hydroxy group or a nitro group,
and their salts of inorganic or organic bases.

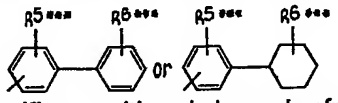
A further modification of the Invention consists of acylbiphenylylaminoalkanoic acids of the general formula I***



in which
R^{1***} signifies an aliphatic hydrocarbon radical with 1 to 3 carbon atoms or a phenyl radical

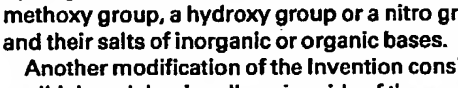


A*** signifies a group of the formula

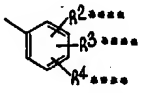


n*** signifies a positive whole number from 3 to 5,
R^{2***} signifies a hydrogen atom,
R^{3***} and R^{4***} are the same or different and signify a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxy group, a methoxy group or a trifluoromethyl group,
one of the substituents R^{5***} or R^{6***} signifies a hydrogen atom and the other signifies a hydrogen atom or a methoxy group,
and their salts of inorganic or organic bases.

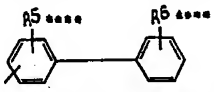
A preferred form of embodiment of the Invention consists of acylbiphenylylaminoalkanoic acids of the general formula I****.



in which
R^{1****} signifies an alkyl group with 1 to 3 carbon atoms, an alkenyl group with 2 or 3 carbon atoms or a phenyl group



A**** signifies a group of the formula



n**** signifies a positive whole number from 3 to 5,
R^{2****} signifies a hydrogen atom,
R^{3****} signifies a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxy group, a methoxy group or a trifluoromethyl group,
R^{4****} signifies a hydrogen atom or a chlorine atom,
one of the substituents R^{5****} or R^{6****} signifies a hydrogen atom, and the other signifies a hydrogen atom or a methoxy group,
and their pharmacologically compatible salts of inorganic or organic bases.

Particularly preferred representatives of the forms of embodiment I**** are those in which R^{3****} signifies a fluorine atom, a chlorine atom, a hydroxy group or a methoxy group, R^{5****} and R^{6****} signify hydrogen atoms, A****, R^{1****}, n****, R^{2****} and R^{4****} have the meaning indicated above, and their pharmacologically compatible salts of inorganic or organic bases.

Further especially preferred representatives of the forms of embodiment I*** or I**** are those in which A*** or A**** have the meaning of a 2-biphenylyl radical, and their pharmacologically compatible salts of inorganic or organic bases.

As compounds comprised by the general formula I one may mention by way of example
4-[4-methoxy-N-(2'-fluoro-biphenyl-2-yl)-benzamido]-butyric acid,
4-[2,4-dichloro-N-(6-methyl-biphenyl-2-yl)-benzamido]-butyric acid,
4-[N-(2'-ethyl-biphenyl-2-yl)-n-butyramido]-butyric acid,
4-[3-fluoro-4-methyl-N-(3,2'-dimethyl-biphenyl-2-yl)-benzamido]-butyric acid,
4-[3,5-dimethoxy-N-(4-chloro-biphenyl-3-yl)-benzamido]-butyric acid,
4-[N-(4,4'-dimethyl-biphenyl-3-yl)-hexanoylamido]-butyric acid,
4-[3-trifluoromethyl-N-(6-ethoxy-biphenyl-3-yl)-benzamido]-butyric acid,
4-[2-bromo-N-(2'-methoxy-biphenyl-4-yl)-benzamido]-butyric acid,
4-[3-methoxy-4-methyl-N-(4'-methoxy-biphenyl-4-yl)-benzamido]-butyric acid,
5-[4-methyl-3-nitro-N-(biphenyl-2-yl)-benzamido]-valeric acid,
5-[3-chloro-N-(4'-methoxy-biphenyl-4-yl)-benzamido]-valeric acid,
5-[4-fluoro-N-(6-ethoxy-biphenyl-3-yl)-benzamido]-valeric acid,
5-[4-methoxy-N-(2'-fluoro-biphenyl-2-yl)-benzamido]-valeric acid,
5-[N-(4'-chloro-biphenyl-4-yl)-methacryloylamido]-valeric acid,
6-[2-methoxy-N-(6-methyl-biphenyl-2-yl)-benzamido]-caproic acid,
6-[3,5-dichloro-N-(4,4'-dimethyl-biphenyl-3-yl)-benzamido]-caproic acid,
6-[2,4-dimethyl-N-(4'-chloro-biphenyl-4-yl)-benzamido]-caproic acid,
6-[3-methoxy-4-methyl-N-(2'-fluoro-biphenyl-2-yl)-benzamido]-caproic acid,
6-[4-nitro-N-(biphenyl-2-yl)-benzamido]-caproic acid,
6-[N-(4'-ethoxy-biphenyl-4-yl)-isovaleroylamido]-caproic acid.

Preferred representatives of the compounds according to the Invention are
4-[4-chloro-N-(biphenyl-2-yl)-benzamido]-butyric acid,
4-[N-(biphenyl-2-yl)-acetamido]-butyric acid,
4-[4-fluoro-N-(biphenyl-2-yl)-benzamido]-butyric acid,
4-[N-(biphenyl-2-yl)-crotonoylamido]-butyric acid,
6-[4-chloro-N-(biphenyl-2-yl)-benzamido]-caproic acid,
6-[2,4-dichloro-N-(biphenyl-2-yl)-benzamido]-caproic acid,
6-[5-chloro-2-methoxy-N-(biphenyl-2-yl)-benzamido]-caproic acid,
5-[2-hydroxy-N-(biphenyl-2-yl)-benzamido]-valeric acid and their salts.

The compounds according to the Invention display valuable pharmacological properties which make them commercially utilisable. In warm-blooded animals they develop a protective action for stomach and liver, and in addition they bring about an increase in the secretion of the pancreas and liver (bile). In addition they bring about an inhibition of the formation of glucose from lactate and pyruvate in the liver.

Because of their advantageous activity, the acylbiphenylylaminoalkanoic acids are suitable for the treatment and prophylaxis of diseases which are attributable to disorders of the stomach or intestine or to reduced performances of the pancreas, bile and/or liver. For example one treats gastric or intestinal ulcers, Billroth II, pancreatic insufficiency, sprue, indigestions and malabsorptions of different aetiology, acute and chronic pancreatitis, indirect disorders of the pancreatic function (supporting of the production of secretin and pancreozymin), as well as gall bladder and bile duct inflammations, disorders of the bile flow, motility disorders of the bile ducts, a feeling of repletion, flatulence, constipation, upper abdominal complaint, hepato-biliar functional disorders, acute and chronic hepatitis, intoxications of the liver, fatty degeneration of the liver, diabetes (maturity onset diabetes), insulin deficiency diabetes in the form of "brittle diabetes", late diabetic damage.

The Invention thus furthermore relates to a process for the treatment of mammals suffering from one or more of the above-mentioned diseases. The process is characterised in that a therapeutically active and pharmacologically tolerated amount of one or more compounds of the general formulae I, I*, I**, I*** and I**** and/or salts thereof is administered to the sick mammal. The Invention also relates to the use of the compounds according to the Invention in combating the illnesses indicated above. The Invention likewise comprises the use of the compounds according to the Invention for the preparation of medicaments which are employed for combating the illnesses listed.

The Invention further relates to pharmaceutical products which contain one or more of the acylbiphenylylaminoalkanoic acids of the general formula I

$$R^1-CO-\underset{\displaystyle A}{\underset{|}{N}}-C_nH_{2n}-COOH \qquad (I),$$

in which
R^1 signifies an aliphatic or alicyclic hydrocarbon radical or an optionally substituted phenyl group,
A signifies an optionally substituted and/or hydrogenated biphenylyl radical,
n signifies a positive whole number from 3 to 5,
and/or their pharmacologically compatible salts of inorganic or organic bases.

Forms of embodiment of the pharmaceutical products are those which contain acylbiphenylylaminoalkanoic acids of the formulae I*, I**, I***, I****, or their preferred representatives and/or their pharmacologically compatible salts of inorganic or organic bases.

The pharmaceutical products are produced according to known processes. As pharmaceutical products the new compounds can be used as such or if desired in combination with suitable pharmaceutical carriers. If the new pharmaceutical preparations in addition to the active principles contain pharmaceutical carriers, the active principle content of these

mixtures is 1 to 95, preferably 15 to 85 per cent by weight of the total mixture.

In accordance with the Invention it is possible in the field of human and veterinary medicine to use the active principles in any desired form, for example systemic, provided that the formation or maintenance of adequate blood or tissue levels or local concentrations of active principle is ensured. This can either be carried out by oral, rectal or parenteral administration in suitable doses. More advantageously the pharmaceutical preparation of the active principle occurs in the form of unit doses which are designed for the particular form of administration desired. A unit dose can be , for example, a tablet, a pill, a capsule, a suppository, or a measured volume of a powder, a granulate, a solution, an emulsion, a suspension, a sol or a gel.

"Unit dose" in the sense of the present Invention is to be understood to mean a physically determined unit which contains an individual quantity of the active component in combination with a pharmaceutical carrier, the active principle content of which corresponds to a fraction or multiple of the therapeutical individual dose. An individual dose preferably contains the quantity of active principle which is dispensed in a single application and which corresponds usually to a whole, a half or a third or a quarter of the daily dose. If for an individual therapeutical administration only a fraction, such as a half or a quarter of the unit dose is required, the unit dose is advantageously divisible, for example in the form of a tablet with a notch for breaking.

The pharmaceutical preparations according to the Invention, if they occur in unit doses and are intended for application, for example to human beings, may contain 0.5 to 1000 mg, advantageously 1 to 750 mg and especially 5 to 500 mg of active principle.

Generally speaking, it has been found advantageous both in human medicine and in veterinary medicine, to administer the active principle or principles in oral administration in a daily dose of 0.01 to 40, preferably 0.1 to 30, especially 0.2 to 20 mg/kg body weight, possibly in the form of several, preferably 2 to 3 individual administrations, in order to achieve the desired results. An individual administration contains the active principle or principles in quantities of 0.01 to 20, preferably 0.1 to 15, especially 0.2 to 10 mg/kg body weight.

In a parenteral treatment, for example intromuscular or intravenous application, it is possible to use similar dosages. With this therapy one applies 50 to 1000 mg of active principle.

The therapeutical administration of the pharmaceutical preparation is carried out in the case of long-term medication generally at fixed points of time, such as 1 to 4 times a day, for example before or after meals and/or in the evening. In the case of acute attacks the medication is carried out at varying points of time. Under certain circumstances it may be necessary to differ from the said dosages, namely according to the nature, the body weight and the age of the patient to be treated, the nature and severity of the disease, the nature of the preparation and the application of the drug as well as the period of time or interval within which the administration takes place. Thus in some cases it may be sufficient to manage with less than the above-mentioned quantity of active principle, whereas in other cases the quantity of active principle mentioned above must be exceeded. The determination of the optimum dosage and type of application of the active principles necessary in each case can at any time be carried out by the expert on the basis of his technical knowledge.

The pharmaceutical preparations consist as a rule of the active principles according to the Invention and non-toxic pharmaceutically compatible drug excipients which are used as an admixture or diluent in the solid, semi-solid or liquid form or as an encapsulating agent, for example in the form of a capsule, a tablet coating, a bag or another container, for the therapeutically active component. An excipient can, for example, serve as a vehicle for the uptake of the medicament by the body, as a formulation aid, as a sweetening agent, as a flavour corrector, as a colouring material or as a preservative. The carriers are in each instance adapted by the specialist to the diseases which are to be treated with the pharmaceutical preparations.

For oral use it is possible to use, for example, tablets, pills, hard and soft capsules, for example of gelatine, dispersible powders, granulates, aqueous and oily suspensions, emulsions, solutions or syrups.

Tablets can contain inert diluents, for example calcium carbonate, calcium phosphate, sodium phosphate or lactose; granulating and distributing agents, for example maize starch or alginates; binders such as for example starch, gelatine or gum acacia; and lubricants, such as for example aluminium or magnesium stearate, talcum or silicone oil. They can also be provided with a coating which can also be designed in such a way that it gives a delayed dissolution and resorption of the drug in the gastrointestinal tract and therefore ensures, for example, a better compatibility, protraction or retarding. Gelatine capsules can contain the pharmaceutical product mixed with a solid diluent, for example calcium carbonate or kaolin, or an oily diluent, for example olive oil, groundnut oil or liquid paraffin.

Aqueous suspensions can contain suspension agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylcellulose, sodium alginate, polyvinylpyrrolidone, gum dragon or gum acacia; dispersants and wetting agents, for example polyoxyethylene stearate, heptadecaethylene oxycetanol, polyoxyethylene sorbitol monooleate, polyoxyethylene sorbitan monooleate or lecithin; preservatives, such as for example methyl or propyl hydroxybenzoates; flavouring materials; sweetening agents, for example sodium cyclamate, saccharin.

Oily suspensions can contain for example groundnut oil, olive oil, sesame oil, coconut oil or liquid paraffin and thickeners such as for example beeswax, paraffin wax or cetyl alcohol; also they may contain sweeteners, flavouring materials and anti-oxidants.

Powders and granulates which are dispersible in water can contain the pharmaceutical products in admixture with dispersants, wetting agents and suspending agents, for example those mentioned above, as well as sweeteners, flavouring materials and colouring materials.

Emulsions can contain, for example, olive oil, groundnut oil or liquid paraffin as well as emulsifiers, such as for example gum acacia, gum dragon, phosphatides, sorbitan monooleate, polyoxyethylene sorbitan monooleate, and sweeteners and flavouring materials.

For rectal use of the pharmaceutical products one uses suppositories, which are produced with the help of binders which melt at rectal temperature, for example cocoa butter or polyethyleneglycols.

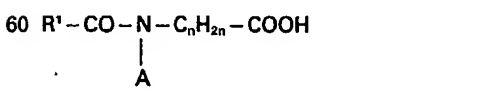
For parenteral use of the pharmaceutical products one uses sterile injectable aqueous suspensions, isotonic saline solution or other solutions which can contain dispersants or wetting agents and/or pharmacologically compatible diluents, for example propyleneglycol or butyleneglycol.

The active principle or principles can if desired be formulated with one or more of the said carrier materials or additives also in a microencapsulated form.

If the acylbiphenylylaminoalkanoic acids according to the invention and/or their salts are to be used for the treatment of diseases which are based on disorders of the stomach or intestine or on reduced performances of the pancreas, bile and/or liver, the pharmaceutical preparations can also contain one or more other pharmacologically active components of other groups of pharmaceutical products, such as antacids, for example aluminium hydroxide, magnesium aluminate; tranquilizers, such as benzodiazepines, for example Diazepam; spasmolytics, such as for example Bietamiverin, Camylofin; anticholinergics, such as for example oxyphencyclimine, phencarbamide; despumation agents, for example dimethylpolysiloxane; laxatives, for example Bisacodyl; swelling agents; if desired also ferments, bile acids, antibiotics, vitamins, amino acids or fatty acid mixtures.

If the acylbiphenylylaminoalkanoic acids and/or their salts are formulated as antidiabetic products, the pharmaceutical preparations can also contain one or more pharmacologically active components belonging to different groups of pharmaceutical products, such as additional antidiabetics (sulphonamides, sulphonyl ureas), for example carbutamide, tolbutamide, chlorpropamide, glibenclamide, glibornuride, glisoxepide, gliquidone, glymidine, or hypolipidaemics, such as benzafibrat or nicotinic acid as well as their derivatives and salts.

A further object of the invention is a process for the production of acylbiphenylylaminoalkanoic acids of the general formula I



(I),

in which

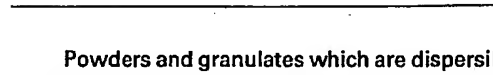
R^1 signifies an aliphatic or alicyclic hydrocarbon radical or an optionally substituted phenyl group,

A signifies an optionally substituted and/or hydrogenated biphenyl radical,

n signifies a positive whole number from 3 to 5,

and their salts of inorganic and organic bases, which is characterised by the fact that

a) a biphenylylaminoalkanoic acid of the general formula II



(II),

in which A and n habe the meanings given above, if desired with protection of the carboxyl group, is acylated with an acyl derivative of the general formula III

(III),

in which R^7 signifies a leaving group or a R^1–CO–O– group, and R^1 has the meaning given above, and if desired is then converted into a salt or else

b) a biphenylylaminoalkenoic acid of the general formula IV

(IV),

in which R^1, A and n have the meanings given above, is hydrogenated, if desired with protection of the carboxyl group, and if desired is then converted into a salt or

c) a functional acylbiphenylylaminoalkanoic acid derivative of the general formula V

(V),

in which R^1, A and n have the meanings given above and G signifies a functional derivative of a carboxyl group, is solvolysed and if desired is then converted into a salt.

For the production of the compounds of modifications I*, I**, I*** or I**** corresponding initial materials II*, II**, II*** or II****; III*, III**, III*** or III****; IV*, IV**, IV*** or IV**** or V*, V**, V*** or V**** in which the substituents have the corresponding meaning, are reacted.

If the biphenylylaminoalkanoic acids of the formula II are reacted with the protection of the carboxyl group, those representatives are used the protective groups of which do not react with the acyl derivatives III. Suitable representatives are for example esters of alkanols, including those with 1 to 5 carbon atoms, or phenalkanols, such as methyl, propyl, butyl, benzyl or phenethyl esters, possibly also solutions with inorganic or organic bases, such as alkali or alkaline earth metal hydroxides, ammonia, tertiary nitrogen bases (for example triethylamine, pyridine).

In the acyl derivatives III a leaving group R^7 is for example a hydroxy group, a halogen atom, preferably a chlorine or bromine atom, an alkylsulphonyloxy or benzenesulphonyloxy group, such as a mesyloxy or p-tolylsulphonyloxy group, an alkoxy group, preferably a methoxy or ethoxy group, an

alkylmercapto group, such as a methylmercapto or ethylmercapto group.

The reaction of the biphenylylaminoalkanoic acids II with the acyl derivatives III is carried out by known processes. The reaction is carried out in suitable solvents, such as water or hydrocarbons, for example benzene, toluene, xylene, or ethers, for example tetrahydrofuran, dioxan, 1,2-dimethoxyethane, or ketones, for example methylethylketone, or amides, for example dimethylformamide, or sulphoxides, for example dimethylsulphoxide.

Expediently the acylation, if R^7 signifies a leaving group, is carried out in the presence of an acid-binding agent (proton acceptor). Suitable as such one may mention by way of example alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, or alkali metal carbonates such as sodium carbonate, potassium carbonate, or tertiary amines such as pyridine, triethylamine, ethyldiisopropylamine. If the acyl derivatives III are acid anhydrides, that is to say if R^7 signifies the R^1–CO–O– group, it is also sufficient to heat the compounds II and III in an inert solvent.

The reaction can be varied within wide limits, for example –20 to +100°C, temperatures around room temperature (10 to 30°C) being preferred. If the compounds II are acylated with the protection of the carboxyl group, then after the acylation the protective group is split off again in the usual manner. If salts are used as protective group, the liberation of the acids I obtained is effected by reaction with a suitable mineral acid, such as hydrochloric acid, or sulphuric acid. If esters are used as protective groups, the acylation is followed by the saponification of the reaction product to give compounds of the formula I. The saponification is preferably carried out with an alcoholic (for example ethanolic) alkali metal hydroxide (for example potassium hydroxide) solution at room temperature, optionally with the addition of an inert diluent such as dioxan or benzene.

The initial compounds of the formula II are produced by various processes which are in themselves known. Thus, they are obtained by reacting halogenalkanoic acids of the formula VI, preferably with the protection of the carboxyl group as an ester group, with a biphenylylamine of the formula VII

$$R^8-C_nH_{2n}-COOH \qquad A-NH_2$$

(VI) (VII),

in which n and A have the meanings given above and R^8 signifies a halogen atom, preferably a chlorine or bromine atom. The reaction is expediently carried out in the presence of an inert solvent, for example benzene, cyclohexane, diethyl ether, with the addition of a proton acceptor. One may use for this purpose, for example, an excess of the amine VII used for the reaction. If desired, however, it is also possible to add a different proton acceptor.

The starting products II are also obtained by reacting an alkanoic acid ester VIII

$$CH_2=CH-C_{n-2}H_{2n-4}-CO-O-R^9 \qquad \text{(VIII)},$$

in which n has the meaning given above and R^9 signifies an alkyl group with 1 to 5 carbon atoms or a benzyl group, with a biphenylylamine VII. The reaction is expediently carried out in the presence of an inert solvent, such as hydrocarbons, for example benzene, toluene, xylene or ethers, for example tetrahydrofuran, dioxan, 1,2-dimethoxyethane, or ketones, for example methylethylketone, or amides, for example dimethylformamide, or sulphoxides, for example dimethylsulphoxide, or nitriles, for example acetonitrile. Expediently the reactants are heated in the solvent, for example by boiling under reflux.

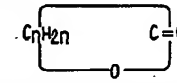
The protective group R^9 is expediently split off only after the reaction of the resultant intermediate products II with the acyl derivatives III so as to obtain the end products I.

The initial compounds II are also obtained by the solvolysis of functional biphenylylaminoalkanoic acid derivatives of the general formula IX

$$A-NH-C_nH_{2n}-G \qquad \text{(IX)},$$

in which A, n and G have the meanings given above, by means of processes which are known to the technician. Expedient forms of execution are described under process variant c).

The starting products II are further obtained by reacting biphenylylamines VII with lactones of the general formula X



(X)

in which n has the meaning given above, in a known manner. The reaction is carried out for example by heating the reactants VII and X (e.g. to the boiling point of the solvent) in inert solvents such as ethers, for example diethyl ether, tetrahydrofuran or nitriles, for example acetonitrile. The acid obtained can then be converted if desired into the corresponding esters, for example by heating in the corresponding alcohols in the presence of a mineral acid, such as hydrochloric acid or sulphuric acid.

The intermediate products II are alternatively obtained in a known manner by the hydrogenation of biphenylyliminoalkanoic acids XI

$$A-N=CH-(CH_2)_{n-1}-COOH \qquad \text{(XI)}$$

in which A and n have the meaning given above, optionally with the protection of the carboxyl group in a known manner. The hydrogenation is carried out for example with Raney nickel under hydrogen pressures of 1 to 250 atmospheres at room temperature in absolute ethanol.

The acids XI are accessible by reacting the biphenylylamines VII with oxo-acid esters XII

$$O=CH-(CH_2)_{n-1}-CO-O-R^9 \qquad \text{(XII)},$$

in which n and R^9 have the meanings given above.

The hydrogenation according to process variant b) is carried out according to methods such as are known to the technician. Thus the biphenylylaminoalkenoic acids IV are hydrogenated with hydrogen in the presence of a transition metal or noble metal catalyst or the corresponding oxides

or complexes in inert solvents. Suitable metals, for example, are platinum, palladium, iridium, rhodium. A summary of the hydrogenation process is to be found inter alia in Kirk-Othmer *11*, 418-462; Ullmann *10*, 109-114, 541-555; *14*, 630-649. The splitting off of any protective group which may be present is carried out in the usual manner.

The alkenoic acids IV are obtained for example from the halogenalkenoic acid esters XIII

$$R^{10}-C_nH_{2n-2}-CO-O-R^9 \qquad (XIII),$$

in which R^9 and n have the meanings given above and R^{10} signifies a halogen atom, preferably a bromine atom, by amination with a biphenylylamine VII, acylation with an acyl derivative III and if desired subsequent saponification. The production is carried out by known methods, halogenation (production of XIII) and amination, for example analogous to J. Heterocycl. Chem. 8 (1971) 21; acylation and saponification are carried out analogously to the description of the present Application.

The halogenalkanoic acids VI and biphenylylamines VII are known compounds or are produced by analogy processes; for example the halogenalkanoic acids VI are accessible by sovolysis, such as hydrolysis or alcoholysis, of the corresponding lactones and subsequent halogenation. The biphenylylamines VII are obtained by the reduction of corresponding nitro compounds which are accessible by the nitration of corresponding biphenyls.

The solvolysis according to process variant c) is carried out by processes known to the technician. A functional acid derivative in this case is understood to mean a derivative whose functional group G can be converted by solvolysis into the free carboxyl group. Typical representatives are for example those in which G signifies a –CN group or a $-C\begin{matrix}X\\ \diagdown\\ Y\end{matrix}$ which

X signifies an oxygen or a sulphur atom or a substituted nitrogen atom, especially an imino, alkylimino or hydroxyimino group and

Y signifies a hydroxy group or a monovalent eliminable electrophilic radical, especially a free or substituted amino group, preferably a monoalkyl or dialkyl or aryl amino group, a hydroxyamino or hydrazino group, a hydrazobenzene group, a 2-hydroxyethylamino group, a free or substituted mercapto group, preferably an alkylthio group, a substituted hydroxy group, preferably an alkoxy group, an azido, a chloro or bromo radical, a morpholino group or a piperidino group, in which Y is not a hydroxy group if X represents an oxygen atom.

An alkyl radical of an alkylimino, a monoalkylamino, a dialkylamino, an alkylthio and an alkoxy group is to be understood to mean an alkyl radical with up to 5 carbon atoms, whilst an aryl radical of an arylamino group is to be understood to mean an aryl radical with up to 10 carbon atoms.

Preferred representatives of the acid derivative V are those in which G signifies a –CN group or a $-C\begin{matrix}X\\ \diagdown\\ Y\end{matrix}$ group, in which

X signifies an oxygen atom, a sulphur atom or an imino group and

Y signifies an amino, monoalkylamino, dialkylamino, phenylamino, alkoxy, alkylthio, chloro or bromo radical.

Particularly preferred representatives of the acid derivative V are the corresponding acid amides, alkyl esters of the acid and nitriles, that is to say those compounds of the formula V in which G represents a $-CO-NH_2$, $-CO-NH-R^9$, $-CO-NR^9{}_2$, $-CO-O-R^9$ or –CN group and R^9 has the meaning given above. They constitute valuable intermediate products for the production of the compounds I and their salts.

For the solvolysis of the functional carboxylic acid derivatives V one uses a medium which gives off water, which consists wholly or partly of water or of agents which split off water under hydrolysis conditions. The reaction can be carried out as a homogeneous reaction, in which case one usually operates in the presence of a polar organic solvent or a solutizer. Advantageously one uses as solvent, for example, low-molecular alcohols, dioxan, acetone, low-molecular carboxylic acids, N-methylpyrrolidone, sulpholan or dimethylsulphoxide. However, it is also possible to carry out the hydrolysis as a heterogeneous reaction. The pH of the medium which splits off water depends upon the chemical nature of the acid derivative used, but also on the nature of the compound of the general formula I which is desired and it can therefore be neutral, acid or basic. It is adjusted to the desired value with acids, bases or buffers.

The hydrolysis temperatures are between 0°C and the boiling point of the medium which splits off water, generally between 0° and 150°C, and especially between 20 and 120°C. The hydrolysis temperatures depend individually also on whether one operates under pressure or without pressure. The reaction times are between 10 minutes and 20 hours according to the charge, the reaction temperatures and other reaction parameters. After the hydrolysis has ended, the acids I are isolated by using the usual methods, for example by recrystallisation or by the acidification of their solutions, if desired with the concentration of their solutions. In order to purify it, their alkaline solution can be extracted with an organic solvent which is not miscible with the alkaline solution, for example diethyl ether, benzene, chlorobenzene, chloroform or methylene chloride.

The carboxylic acid derivatives V are obtained by methods which are current to the technician. For example they are obtained by the reaction of functional halogenalkanoic acid derivatives XIV

$$R^8-(CH_2)_n-G \qquad (XIV),$$

in which R^8, n and G have the meanings given above, with biphenylylamines VII followed by acylation with acyl derivatives III.

The conversion of the acids of the general formula I or of the modifications I*, I**, I***, I*** into their salts can be carried out by direct alkaline hydrolysis of the acid derivatives of the formula V. As alkaline reactant one uses the particular inorganic or organic base whose salt is desired. However, one also obtains the salts if one reacts the acids of the general

formula I with the stoichiometrical equivalent of corresponding base, for example sodium hydroxide or sodium alcoholate, or else readily soluble salts are converted by double decomposition into sparingly soluble salts, or else any salts are converted into pharmacologically compatible salts.

The following Examples illustrate the invention in greater detail, but without restricting it. The abbreviations MP and BP signify melting point and boiling point respectively.

EXAMPLE 1

4-[p-chloro-N-(biphenyl-2-yl) benzamido] butyric acid

R^1 = *p*-chlorophenyl, A = biphenyl-2-yl, n = 3

a) *Ethyl 4-(biphenyl-2-yl) aminobutyrate*

30.0 g of 2-aminobiphenyl, 23.4 g of ethyl diisopropylamine and 35.4 g of ethyl 4-bromobutyrate are heated together to 150° for 3 hours while stirring. After cooling, the reaction product is stirred with diethyl ether, the precipitated salt is filtered off, and the residue (remaining after evaporating off the ether) is recrystallized from isopropyl alcohol to obtain 32.0 g (63.7% of theory) of ethyl 4-(biphenyl-2-yl) amino butyrate, MP 60° to 62°.

b) *Ethyl 4-[p-chloro-N-(biphenyl-2-yl) benzamido] butyrate*

9.8 g of *p*-chlorobenzoyl chloride is added drop by drop at room temperature (while stirring and within 30 minutes) to a solution of 16.0 g of ethyl 4-(biphenyl-2-yl)-aminobutyrate and 7.3 g of ethyl diisopropylamine in 70 ml of benzene. After a further hour, the precipitate is filtered off, the filtrate is evaporated, and the evaporation residue is recrystallized from cyclohexane to obtain 18.0 g (75.6% of theory) of ethyl 4-[(*p*-chloro-N-(biphenyl-2-yl) benzamido] butyrate, MP 100° to 102°.

c) *4-[p-chloro-N-(biphenyl-2-yl) benzamido] butyric acid*

15.0 g of ethyl 4-[*p*-chloro-N-(biphenyl-2-yl) benzamido]-butyrate is dissolved in 100 ml of benzene and, after the addition thereto of a solution of 2.8 g of potassium hydroxide in 20 ml of ethanol, is then stirred at room temperature for 5 hours. The solvent is then distilled off *in vacuo*, and the obtained residue is dissolved in water. The resulting aqueous solution is acidified with dilute hydrochloric acid, and the precipitate, which separates out, is taken up in methylene chloride. The residue remaining, after drying and distilling off the methylene chloride, is recrystallized from an ethanol/water mixture (2:1) to obtain 10.1 g (72.1% of theory) of 4-[*p*-chloro-N-(biphenyl-2-yl) benzamido] butyric acid, MP 135° to 137°.

EXAMPLE 2

4-[m-trifluoromethyl-N-(biphenyl-2-yl) benzamido] butyric acid

R^1 = α, α, α-trifluoro-*m*-tolyl, A = biphenyl-2-yl, n = 3

a) *Ethyl 4-[m-trifluoromethyl-N-(biphenyl-2-yl) benzamido] butyrate*

Analogously to Example 1 b, 11.8 g of ethyl 4-(biphenyl-2-yl) aminobutyrate and 5.4 g of ethyl-diisopropylamine are reacted in 70 ml of benzene with 8.7 g of *m*-trifluoromethylbenzoyl chloride. The reaction product is recrystallized from a mixture of isopropyl alcohol and water (1:1) to obtain 16.0 g (84.4% of theory) of ethyl 4-[*m*-trifluoromethyl-N-(biphenyl-2-yl) benzamido]-butyrate, MP 65° to 67°.

b) *4-[m-trifluoromethyl-N-(biphenyl-2-yl) benzamido] butyric acid*

16.0 g of ethyl 4-[*m*-trifluoromethyl-N-(biphenyl-2-yl)-benzamido] butyrate in 50 ml of benzene are mixed with a solution of 3.4 g of potassium hydroxide in 25 ml of ethanol and stirred at room temperature for 8 hours. When further processed analogously to Example 1 c, 13.7 g (91.3% of theory) of 4-[*m*-trifluoromethyl-N-(biphenyl-2-yl) benzamido] butyric acid, MP 156° to 157°, are obtained.

EXAMPLE 3

4-[p-fluoro-N-(biphenyl-2-yl) benzamido] butyric acid

R^1 = *p*-fluorophenyl, A = biphenyl-2-yl, n = 3

a) *Ethyl 4-[p-fluoro-N-(biphenyl-2-yl) benzamido] butyrate*

Analogously to Example 1 b, 10.0 g of ethyl 4-(biphenyl-2-yl) aminobutyrate and 4.6 g of ethyl-diisopropylamine in 50 ml of benzene are reacted with 5.6 g of *p*-fluorobenzoyl chloride. The reaction product is recrystallized from cyclohexane to obtain 12.1 g (84.6% of theory) of ethyl 4-[*p*-fluoro-N-(biphenyl-2-yl)-benzamido butyrate, MP 83° to 84°.

b) *4-[p-fluoro-N-(biphenyl-2-yl) benzamido] butyric acid*

11.2 g of ethyl 4-[*p*-fluoro-N-(biphenyl-2-yl) benzamido]-butyrate in 50 ml of benzene is mixed with a solution of 2.2 g of potassium hydroxide in 20 ml of ethanol and stirred at room temperature for 8 hours. When processed analogously to Example 1 c, 7.1 g (71.7% of theory) of 4-[*p*-fluoro-N-(biphenyl-2-yl) benzamido] butyric acid, MP 120° to 122°, are obtained.

EXAMPLE 4

4-[5-chloro-2-methoxy-N-(biphenyl-2-yl) benzamido] butyric acid

R^1 = 5-chloro-2-methoxyphenyl, A = biphenyl-2-yl, n = 3

Analogously to Example 1, 10.0 g of ethyl 4-(biphenyl-2-yl) aminobutyrate and 4.6 g of ethyl-diisopropylamine in 50 ml of benzene are reacted with a solution of 7.3 g of 5-chloro-2-methoxybenzoyl chloride in 20 ml of benzene to obtain, as reaction product, 15.0 g (94.1% of theory) of ethyl 4-[5-chloro-2-methoxy-N-(biphenyl-2-yl) benzamido] butyrate as a viscous non-distillable oil. The saponification of this ester yields 12.4 g (88% of theory) of 4-[5-chloro-2-methoxy-N-(biphenyl-2-yl) benzamido] butyric acid, MP 160° to 162°.

EXAMPLE 5

4-[N-(biphenyl-2-yl) acetamido] butyric acid

R^1 = $-CH_3$, A = biphenyl-2-yl, n = 3

Analogously to Example 1, 16.0 g of ethyl 4-(biphenyl-2-yl) aminobutyrate and 7.3 g of ethyl-diisopropylamine in 70 ml of benzene are reacted with 4.4 g of acetyl chloride to obtain, as reaction product, 14.0 g (76.2% of theory) of ethyl 4-[N-(biphenyl-2-yl) acetamido] butyrate as a viscous non-distillable oil. The saponification of this ester

and recrystallization of the crude product obtained from isopropyl alcohol yields 10.1 g (79.0% of theory) of 4-[N-(biphenyl-2-yl) acetamido] butyric acid, MP 124° to 125°.

EXAMPLE 6

4-[N-(biphenyl-2-yl) crotonoylamido] butyric acid

$R^1 = CH_3-CH=CH-$, A = biphenyl-2-yl, n = 3

Analogously to Example 1, 10.0 g of ethyl 4-(biphenyl-2-yl) aminobutyrate and 4.6 g of ethyldiisopropylamine in 70 ml of benzene are reacted with 3.8 g of crotonyl chloride to obtain, as reaction product, 10.1 g (81.5% of theory) of ethyl 4-[N-(biphenyl-2-yl) crotonoylamido] butyrate as a viscous non-distillable oil. The saponification of this ester and recrystallization of the crude product obtained from isopropyl alcohol yields 5.1 g (55% of theory) of 4-[N-(biphenyl-2-yl) crotonoylamido] butyric acid, MP 127° to 128°.

EXAMPLE 7

5-[(p-chloro-N-(biphenyl-2-yl) benzamido] valeric acid

R^1 = *p*-chlorophenyl, A = biphenyl-2-yl, n = 4

50.0 g of 2-aminobiphenyl, 38.2 g of ethyldiisopropyamine and 61.9 g of ethyl 5-bromovalerate are reacted analogously to Example 1 a to obtain 80.0 g of ethyl 5-(biphenyl-2-yl) aminovalerate as a non-crystallizing oil.

30.0 g of this ester is reacted, analogously to Example 1 b, with 13.1 g of ethyldiisopropylamine and 17.1 g of *p*-chorobenzoyl chloride in 70 ml of benzene; the ethyl 5-[*p*-chloro-N-(biphenyl-2-yl) benzamido] valerate obtained as an oily intermediate product is then saponified analogously to Example 1 c to obtain 22.1 g (53.7% of theory) of 5[*p*-chloro-N-(biphenyl-2-yl) benzamido] valeric acid, MP 170° to 173°.

EXAMPLE 8

5-[o-hydroxy-N-(biphenyl-2-yl) benzamido] valeric acid

R^1 = *o*-hydroxyphenyl, A = biphenyl-2-yl, n = 4

15.0 g of ethyl 5-(biphenyl-2-yl) aminovalerate is reacted, analogously to Example 1 b, with 6.6 g of ethyldiisopropylamine and 10.0 g of *o*-acetoxybenzoylchloride in 70 ml of benzene to obtain, as reaction product, 17.0 g (73.4% of theory) of ethyl 5-[*o*-acetoxy-N-(biphenyl-2-yl)-benzamido] valerate as a viscous non-distillable oil. The saponification of this ester yields 9.1 g (63.2% of theory) of 5-[*o*-hydroxy-N-(biphenyl-2-yl) benzamido] valeric acid, MP 138° to 139°.

EXAMPLE 9

6-[p-chloro-N-(biphenyl-2-yl) benzamido] caproic acid

R^1 = *p*-chlorophenyl, A = biphenyl-2-yl, n = 5

20.0 g of 2-aminobiphenyl, 15.3 g of ethyldiisopropylamine and 26.3 g of ethyl 6-bromocaproate are reacted, analogously to Example 1 a, to obtain 36.0 g of ethyl 6-(biphenyl-2-yl) aminocaproate as a non-crystallizing oil. 18.0 g of this ester are reacted, analogously to Example 1 b, with 7.5 g of ethyldiisopropylamine and 10.1 g of *p*-chlorobenzoyl chloride in 70 ml of benzene. The resulting reaction product is purified chromatographically over a silica gel column (eluent: methylene chloride) to obtain 11.5 g (44.2% of theory) of ethyl 6-[*p*-chloro-N-(biphenyl-2-yl) benzamido] caproate as a viscous non-distillable oil. Saponification of this ester yields 8.1 g (75.1% of theory) of 6-[*p*-chloro-N-(biphenyl-2-yl) benzamido] caproic acid, MP 93° to 95°.

EXAMPLE 10

6-[5-chloro-2-methoxy-N-(biphenyl-2-yl) benzamido] caproic acid

R^1 = 5-chloro-2-methoxyphenyl, A = biphenyl-2-yl, n = 5

8.0 g of ethyl 6-(biphenyl-2-yl) aminocaproate and 3.3 g of ethyldiisopropylamine in 50 ml of benzene are reacted with a solution of 5.3 g of 5-chloro-2-methoxy-benzoyl chloride in 20 ml of benzene, analogously to Example 1 a, to obtain, as reaction product, 11.1 g (90% of theory) of ethyl 6-[5-chloro-2-methoxy-N-(biphenyl-2-yl) benzamido] caproate as a viscous non-distillable oil. The saponification of this ester yields 7.0 g (67% of theory) of 6-[5-chloro-2-methoxy-N-(biphenyl-2-yl) benzamido]-caproic acid, MP 164° to 165°.

EXAMPLE 11

6-[N-(biphenyl-2-yl) isobutyramido] caproic acid

$R^1 = -CH(CH_3)_2$, A = biphenyl-2-yl, n = 5

Analogously to Example 10 10.0 g of ethyl 6-(biphenyl-2-yl) aminocaproate, 4.2 g of ethyldiisopropylamine and 3.4 isobutyryl chloride in 70 ml of benzene yields 8.9 g (72.6% of theory) of ethyl 6-[N-(biphenyl-2-yl) isobutyramido] caproate as a viscous non-distillable oil. The saponification of this ester yields 6.1 g (74% of theory) of 6-[N-(biphenyl-2-yl) isobutyramido] caproic acid, MP 120° to 121°.

EXAMPLE 12

4-[p-chloro-N-(biphenyl-4-yl) benzamido] butyric acid

R^1 = *p*-chlorophenyl, A = biphenyl-4-yl, n = 3

a) *Ethyl 4-(biphenyl-4-yl) aminobutyrate*

24.0 g (57.3% of theory) of ethyl 4-(biphenyl-4-yl)-aminobutyrate, MP 82° to 84°, are obtained analogously to Example 1 b, from 25.0 g of 4-aminobiphenyl, 19.2 g of ethyldiisopropylamine and 28.9 g of ethyl 4-bromobutyrate.

b) *4-[p-chloro-N-(biphenyl-4-yl) benzamido] butyric acid*

Analogously to Example 1 b, 10.0 g of ethyl 4-(biphenyl-4-yl) aminobutyrate and 4.6 g of ethyldiisopropylamine in 70 ml of benzene are reacted with 6.2 g of *p*-chlorobenzoyl chloride to obtain 9.4 g (62.9% of theory) of ethyl 4-[*p*-chloro-N-(biphenyl-4-yl) benzamido] butyrate as a viscous non-distillable oil. Saponification of this ester, analogously to Example 1 a, yields 7.0 g (79.7% of theory) of 4-[*p*-chloro-N-(biphenyl-4-yl)-benzamido] butyric acid, MP 192° to 194°.

EXAMPLE 13

4-[p-chloro-N-(6-methoxy-biphenyl-3-yl) benzamido] butyric acid

R^1 = *p*-chlorophenyl, A = 6-methoxybiphenyl-3-yl, n = 3

a) *Ethyl 4-(6-methoxy-biphenyl-3-yl) aminobutyrate*

29.5 g of 5-amino-2-methoxybiphenyl, 19.2 g of ethyldiisopropylamine and 28.9 g of ethyl 4-bromobutyrate are heated together (while stirring) for 4 hours at 125°. After cooling, the resulting reaction product is stirred with diethyl ether and filtered

from the precipitated salt. The residue (remaining after evaporating off the ether) is recrystallized from isopropyl alcohol to obtain 22.5 g (48.5% of theory) of ethyl 4 - (6 - methoxybiphenyl - 3 - yl) aminobutyrate, MP 71° to 72°.

b) *4 - [p - chloro - N - (6 - methoxybiphenyl - 3 - yl) benzamido] butyric acid*

8.0 g of ethyl 4 - (6 - methoxybiphenyl - 3 - yl) aminobutyrate and, 3.3 g of ethyldiisopropylamine in 50 ml of benzene are reacted, analogously to Example 1 b, with 4.6 g of *p*-chlorobenzoyl chloride. The reaction product is dissolved in 50 ml of benzene and, after the addition thereto of a solution of 2.3 g of potassium hydroxide in 20 ml of ethanol, is then stirred for 8 hours at room temperature. After distilling off the solvent, the residue is dissolved in water; the resulting solution is acidified with dilute hydrochloric acid and extracted with diethyl ether. The residue (remaining after evaporating off the ether) is recrystallized from ethyl acetate/petrol ether (1:1) to obtain 8.1 g (73.5% of theory) of 4 - [p - chloro - N - (6 - methoxybiphenyl - 3 - yl) - benzamido] butyric acid, MP 114° to 116°.

EXAMPLE 14

4 - [5 - chloro - 2 - methoxy - N - (6 - methoxybiphenyl - 3 - yl) benzamido] butyric acid

R^1 = 5 - chloro - 2 - methoxyphenyl, A = 6 - methoxybiphenyl - 3 - yl, n = 3

Analogously to Example 13, reacting 7.0 g of ethyl 4 - (6 - methoxybiphenyl - 3 - yl) aminobutyrate with 4.6 g of 5 - chloro - 2 - methoxybenzoyl chloride, followed by saponification of the intermediate product, yields 7.1 g (70.1% of theory) of 4 - [5 - chloro - 2 - methoxy - N - (6 - methoxybiphenyl - 3 - yl) benzamido] - butyric acid, MP 155° to 156°.

EXAMPLE 15

6 - [2, 4 - dichloro - N - (biphenyl - 2 - yl) benzamido] caproic acid

R^1 = 2, 4 - dichlorophenyl, A = biphenyl - 2 - yl, n = 5

Following the procedure of Example 9, but substituting 2, 4 - dichlorobenzoyl chloride for *p*-chlorobenzoyl chloride, yields 6 - [2, 4 - dichloro - N - (biphenyl - 2 - yl) benzamido] - caproic acid, MP 112° to 113°, from ethyl acetate/petrol ether (1:1).

EXAMPLE 16

4 - [p - chloro - N - (1', 2', 3', 4', 5', 6' - hexahydrobiphenyl - 4 - yl) benzamido] butyric acid

R^1 = *p* - chlorophenyl, A = 1', 2', 3', 4', 5', 6' - hexahydrobiphenyl - 4 - yl, n = 3

Following the procedure of Example 1 a-c, but substituting *p* - cyclohexylaniline for 2 - amino - biphenyl, 4 - [p - chloro - N - (1', 2', 3', 4', 5', 6' - hexahydrobiphenyl - 4 - yl) - benzamido] butyric acid, MP 75° to 77°, is obtained from isopropyl alcohol/water (1:1).

EXAMPLE 17

5 - [p - chloro - N - (biphenyl - 2 - yl) benzamido] valeric acid

a) *5 - [N - (biphenyl - 2 - yl) amino] valeric acid*

A solution of 8.0 g of ethyl 5 - (biphenyl - 2 - yl) aminovalerate (see Example 7) in 60 ml of benzene is mixed with a solution of 2.2 g of potassium hydroxide in 20 ml of ethanol. After allowing the resulting admixture to stand for 24 hours at room temperature, the solvent mixture is distilled off *in vacuo*. The residue is then dissolved in water; the obtained aqueous solution is washed with diethyl ether and then acidified with dilute hydrochloric acid. The formed precipitate, which is oily at first, is taken up in dichloromethane. The solvent is then distilled off and the residue recrystallized from ethyl acetate/petrol ether (1:1) to obtain 5.6 g (77.3% of theory) of 5 - [N - (biphenyl - 2 - yl) amino] valeric acid, MP 73° to 75°.

b) *5 - [p - chloro - N - (biphenyl - 2 - yl) benzamido] valeric acid*

5.4 g of 5 - [N - (biphenyl - 2 - yl) amino] valeric acid is dissolved in 40 ml of 0.2 N caustic soda solution. Into the resulting clear solution (while vigorously stirring and constantly controlling the pH) 3.5 g of *p*-chlorobenzoyl chloride is added, drop by drop, while concurrently adding dilute caustic soda solution in order to maintain the pH at between 7 and 8. After the addition of acid chloride is complete, the solution is stirred for a further 30 minutes at pH 8 and then acidified to pH 3 with dilute hydrochloric acid. The precipitate, which is oily at first crystallizes after a time. It is filtered off and recrystallized from isopropyl alcohol to obtain 7.6 g (93% of theory) of 5 - [p - chloro - N - (biphenyl - 2 - yl) benzamido] valeric acid, MP 170° to 173°, which is identical with the compound obtained by the procedure of Example 7.

EXAMPLE 18

Ampoules containing 600 mg of 4 - [p - chloro - N - (biphenyl - 2 - yl) benzamido] butyric acid; size of batch: 250 kg.

25.0 kg of 1, 2 - propyleneglycol and 150.0 kg of double-distilled water are placed in a vessel to which 15.0 kg of 4 - [p - chloro - N - (biphenyl - 2 - yl) benzamido] butyric acid are added. Then, while stirring, caustic soda solution (10 percent by weight NaOH) is slowly added. When a solution is obtained, the pH is adjusted to from 7.5 to 8.0. Sodium pyrosulfite*) is added, and the resulting mixture is stirred until all components have dissolved. Using double-distilled water, the solution is made up to 250 kg. The solution is then charged into 10-ml ampoules and sterilized in an autoclave for 30 minutes at 120°.

EXAMPLE 19

Ampoules containing 600 mg of 4 - [N - (biphenyl - 2 - yl) - crotonoylamido] butyric acid; size of batch: 250 kg.

50.0 kg of 1, 2 - propyleneglycol and 150.0 kg of double-distilled water are placed in a vessel. While stirring, 15 kg of 4 - [N - (biphenyl - 2 - yl) crotonoylamido] butyric acid are added thereto. Then caustic soda solution (10 per cent by weight NaOH) is added, and the resulting mixture is adjusted to a pH of 8.0. Using double-distilled water, it is made up to 250 kg. The solution is charged into 10-ml ampoules and sterilized in an autoclave at 120° for 30 minutes.

EXAMPLE 20

Tablets containing 50 mg of 4 - [p - fluoro - N - (biphenyl - 2 - yl) benzamido] butyric acid.

25.0 kg of 4 - [p - fluoro - N - (biphenyl - 2 - yl) benzamido] - butyric acid, 35.0 kg of lactose and 26.0 kg of maize starch are granulated with 21.5 kg of polyvinylpyrrolidone (molecular weight: approx. 25,000) in about 6 liters of water. The granulate is

*) 0.0625 KG

passed through a sieve with a mesh width of 1.25 mm and, after drying, is admixed with 8.0 kg of carboxymethylcellulose, 2.5 kg of talcum and 1.0 kg of magnesium stearate. The dry granulate is pressed into tablets with a diameter of 8 mm, a weight of 250 mg and a hardness of from 5 to 6 kg.

In a similar manner tablets containing 4-[*p*-chloro-N-(biphenyl-2-yl) benzamido] butyric acid or 4-[N-(biphenyl-2-yl) crotonoylamido] butyric acid are prepared.

EXAMPLE 21

Tablets containing 100 mg of 4-[N-(biphenyl-2-yl)-acetamido] butyric acid.

40.0 kg of 4-[N-(biphenyl-2-yl) acetamido] butyric acid, 24.0 kg of lactose and 16.0 kg of maize starch are granulated with 4.0 kg of polyvinylpyrrolidone (molecular weight: approx. 25,000) in about 5.5 liters of water and then pressed through a sieve with a mesh width of 1.25 mm. After drying, 10.0 kg of carboxymethylcellulose, 4.0 kg of talcum and 2.0 kg of magnesium stearate are admixed therewith. On an eccentric machine the resulting granulate is pressed into tablets with a diameter of 9 mm, a weight of 250 mg and a hardness of from 4 to 5 kg.

EXAMPLE 22

Tablets containing 300 mg of 4-[*p*-chloro-N-biphenyl-2-yl) benzamido] butyric acid.

60.0 kg of 4-[*p*-chloro-N-(biphenyl-2-yl) benzamido]-butyric acid, 12.0 kg of lactose and 8.0 kg of maize starch are granulated with 4.0 kg of polyvinylpyrrolidone (molecular weight: approx. 25,000) in about 6 liters of water and then pressed through a sieve with a mesh width of 1.25 mm. After drying, 10.0 kg of carboxymethylcellulose, 4.0 kg of talcum and 2.0 kg of magnesium stearate are admixed therewith. On a rotary pelleting machine the resulting granulate is pressed into tablets with a diameter of 11 mm, a weight of 500 mg and a hardness of from 6 to 7 kg.

Analogously, tablets are produced which contain 300 mg of 4-[p-chloro-N-(biphenyl-2-yl) benzamido] caproic acid.

EXAMPLE 23

10,000 capsules with an active-principle content of 50 mg are produced from the following components: 500 g of 4-[N-(biphenyl-2-yl) crotonoylamido] butyric acid, 495 g of microcrystalline cellulose and 5 g of amorphous silica. The active principle in finely-powdered form, the cellulose and the silica are thoroughly mixed and packed into hard gelatin (size 4) capsules.

PHARMACOLOGY

The acylbiphenylylamino acids exert a marked protective action on the stomach and liver of rats, and in addition increase the pancreatic and bile secretion of rats, in which they are found to be superior to the known commercial preparations, for example Piprozoline, Carbenoxolone. In addition they bring about an inhibition of the formation of glucose from lactate and pyruvate in the liver of rats, in which they are superior to known commercial preparations, for example Buformin, Phenformin.

In the tables which follow, the compounds investigated are characterised by a serial number which has been allocated as follows:

Serial No.	Name of compound
1	Piprozoline
2	Carbenoxolone
3	Buformin
4	Phenformin
5	4-[N-(biphenyl-2-yl)-acetamido]-butyric acid
6	4-[p-chloro-N-(biphenyl-4-yl)-benzamido]-butyric acid
7	6-[p-chloro-N-(biphenyl-2-yl)-benzamido]-caproic acid
8	4-[m-trifluoromethyl-N-(biphenyl-2-yl)-benzamido]-butyric acid
9	4-[p-fluoro-N-(biphenyl-2-yl)-benzamido]-butyric acid
10	4-[N-(biphenyl-2-yl)-crotonoylamido]-butyric acid
11	5-[p-chloro-N-(biphenyl-2-yl)-benzamido]-valeric acid
12	6-[2,4-dichloro-N-(biphenyl-2-yl)-benzamido]-caproic acid
13	6-[5-chloro-2-methoxy-N-(biphenyl-2-yl)-benzamido]-caproic acid
14	4-[p-chloro-N-(biphenyl-2-yl)-benzamido]-butyric acid
15	5-[o-hydroxy-N-(biphenyl-2-yl)-benzamido]-valeric acid
16	4-[2-methoxy-5-chloro-N-(biphenyl-2-yl)-benzamido]-butyric acid
17	6-[N-(biphenyl-2-yl)-isobutyramido]-caproic acid
18	4-[p-chloro-N-(6-methoxy-biphenyl-3-yl)-benzamido]-butyric acid
19	4-[2-methoxy-5-chloro-N-(6-methoxy-biphenyl-3-yl)-benzamido]-butyric acid
20	4-[p-chloro-N-(1',2',3',4',5',6',-hexahydro-biphenyl-4-yl)-benzamido]-butyric acid.

Table I shows the stomach protective action (reversal of the stomach ulcer caused by the ligature of the pylorus and administering 100 mg/kg of acetylsalicylic acid per os) after intraduodenal application in the rat, the lethal action after intraperitoneal administration in the mouse and also the therapeutical quotient (TQ = LD_{50}/ED_{50}) of representatives of the compounds according to the Invention.

Table I
Stomach protection action

Serial No.	Toxicity LD_{50} (mg/kg) (mouse, i.p.)	Antiulcerogenic action/rat ED_{50}*) mg/kg intraduo - denally	TQ LD_{50}/ED_{50}
2	120	50	2.4
5	750	55	13.6
6	120	14	8.6
7	130	22	5.9
8	110	10	11
9	210	40	5.3
10	300	~ 40	~7.5
11	140	30	4.7
13	> 400 **)	10	>40
14	180	20	9
15	>400	<10	>40
18	120	<10	>12
19	190	21	9

*) Dose which reduces the mean ulcer index by 50%
**) per os, i.p. not applicable

Table II shows investigations regarding the antihepatotoxic action ($ED_{25;50}$) of the compounds according to the Invention after oral application to waking rats and the lethal action after intraperitoneal application on the mouse (LD_{50}) as well as the therapeutical quotients (TQ = LD_{50}/ED_{25} and LD_{50}/ED_{50}).

Table II
Antihepatotoxic effect, toxicity and therapeutical quotient

Serial No.	Toxicity LD_{50} (mg/kg) mouse i.p.	Antihepatotoxic effect ED_{25}*) mg/kg per os	ED_{50}*) Rat	TQ LD_{50}/ED_{25}	TQ LD_{50}/ED_{50}
1	1070**)	200	>300	5.4	<3.6
5	750	<3	15	>250	50
6	120	15	22	8	5.5
7	130	~9	14	~14.4	9.3
8	110	10	30	11	3.7
9	210	1.6	2.8	131.3	75
10	300	1.6	2.8	187.5	107.1
11	140	3	12	46.7	11.7
13	>400***)	10		>40	
14	180	<1	3.5	>180	51.4
17	260	<30		> 8.7	
20	~150	≤10		≥15	

Explanations to Table II:
*) ED_{25} or ED_{50} = dose which shortens the hexobarbital narcosis by 25 and 50% respectively of rats suffering from liver damage from CCl_4.
**) LD_{50} (per os) cited from Herrmann et al. Arzneim. - Forsch. 27 (1977) 467
***) per os, i.p. not applicable

Table III shows for representatives of the compounds according to the Invention the influence on the bile secretion (choleresis) of narcosed rats after the intraduodenal application (ED_{50}) and the lethal action on the mouse (LD_{50}) after intraperitoneal application and also the therapeutical quotient (TQ = LD_{50}/ED_{50}).

Table III
Bile secretion, toxicity and therapeutical quotient

Serial No.	Toxicity LD_{50} (mg/kg) (Mouse i.p.)	Bile secretion ED_{50}***) (mg/kg) (Rat i.d.)	TQ (LD_{50}/ED_{50})
1	1070**	40	26.8
5	750	~15	~ 50
10	300	~10	~30
19	190	1	190

***) ED_{50} = dose which brings about an increase in the bile secretion (liquid volume; 30-min. fraction) by a maximum of 50%
**) LD_{50} (p.o.) cited from Herrmann et al. Arzneim.-Forsch. 27 (1977) 467

Table IV shows, for representatives of the compounds according to the Invention, the influence of the pancreatic secretion of narcotized rats after the intraduodenal application (ED_{50}) and the lethal action on the mouse (LD_{50}) after intraperitoneal application, as well as the therapeutical quotient (TQ = LD_{50}/ED_{50}).

Table IV
Pancreatic secretion, toxicity and therapeutical quotient

Serial No.	Toxicity LD_{50} [mg/kg] (Mouse, i.p.)	Pancreatic secretion ED_{50}*) [mg/kg] (Rat, i.d.)	TQ $[LD_{50}/ED_{50}]$
1	1070**)	35	31
5	750	~2	~375
6	120	1	120
8	110	1	110
9	210	2.5	84
12	~250	1.7	~147
13	>400***)	< 1.0	> 400
14	180	1	180
16	170	2	85
18	120	1.5	80
19	190	5	38
20	~150	1.5	~100

* ED_{50} = dose which brings about an increase in the pancreatic secretion (liquid volume; 30-min. fraction) of a maximum of 50%
**) LD_{50} (per os) cited from Herrmann et al. Arzneim.-Forsch. 27 (1977) 467.
***) per os, i.p. not applicable

Table V shows the results of the investigation of the influence of representatives of the compounds according to the Invention on the formation of glucose from lactate and pyruvate in the isolated perfused liver of fasting rats, the inhibition of the glucose formation being shown for a substance concentration of 0.2 mmole/litre in the perfusate and the ED_{50} – determined from 4 concentrations the range from 0.02 to 1.00 mmol/litre – and the lethal action on the mouse (LD_{50}) after intraperitoneal application.

Table V

Inhibition of the formation of glucose from lactate and pyruvate in the isolated perfused rat liver and toxicity on the mouse

Serial No.	Glucose formatfon % change *)	ED_{50}**) (mg/l)	LD_{50} (i.p.) (mg/kg)
3	-1	>1000	213***)
4	-3	>1000	150****)
14	-79	43	180
7	-99	23	130
8	-77	34	110
9	-51	76	210
11	-89	25	140
12	-93	23	~250

Explanations to Table V:

*) substance concentration of 0.2 mmol/litre in the perfusate

** ED_{50} = dose which brings about an inhibition of the glucose formation of a maximum of 50%

***) cited from Söling H.D., Creutzfeldt, W., Int Biguanid Symp., Aachen 1960, Stuttgart, Thieme Verlag

****) cited from Bertarelli, P., Boll.chim.farm. 97 (1958) 396

The compounds according to the Invention are characterised as compared with the comparison compounds 3 and 4 by a considerably stronger inhibition of the formation of glucose from lactate and pyruvate. Whereas 3 and 4 exert practically no inhibition at the concentrations used, with the compounds according to the Invention it is possible to achieve inhibition effects of up to 99%.

The determination of the pharmacological properties was carried out by the folliwng methods:

Influence on the pancreatic and bile secretion of the narcotized rat

Execution of experiment

Male Sprague-Dawley rats (body weight 250-300 g) are narcotized with 1.2 g/kg urethane i.m. Then the abdominal cavity is opened medially, the bile duct is ligatured shortly above the place where it leads into the duodenum and also near to the hepatic duct, and both sections are catherised towards the liver.

As in the rat all the pancreatic ducts lead out into the central section of the bile duct, it is possible in this way to discharge separately the pancreatic secretion from the distal (ligatured) section and the bile from the proximal section of the bile duct.

The quantities of pancreatic juice and bile juice secreted are measured at intervals of 30 minutes over a period from 2 hours before to 3 hours after the intraduodenal administration of the compounds to be tested (quantity of liquid administered 5 ml/kg).

The body temperature of the animals is maintained at 36 to 38°C by means of electric blankets and radiation; the temperature is monitored rectally.

Evaluation:

The liquid volumes of the 30-minute fractions after the administration of the substance are related in each case to the quantity of bile or pancreatic juice secreted prior to the application of the substance (= 100%, mean of the last two measurements). The maximum percentage increase in the pancreatic or bile secretion is represented according to the dose and from this the ED_{50} is determined by interpolation.

Test for antihepatotoxic effect

Influence on the hexobarbital sleeping period of the rate after liver damage by CCl_4

Execution of test:

On the basis of VOGEL et al. (Arzneim.-Forsch. 25 (1975) 82) liver cell damage is produced in fastening female Sprague-Dawley rats 190±10 g body weight, 10 animals/dose per test batch) by the oral administration of carbon tetrachloride (0.15 ml/kg CCl_4 in 2.5 ml/kg olive oil), and the extent of this damage is determined by the prolongation of the sleeping period induced by hexobarbital sodium (50 mg/ml/kg i.v.; caudal vein, duration of injection 45-60 seconds) 47 hours after the administration of the CCl_4. The compounds to be tested are administered 1 hour prior to the administration of CCl_4 orally in a liquid volume of 10 ml/kg.

Evaluation:

The antihepatotoxic effect of the compounds to be tested (sodium salts in aqueous solution) is determined by the reduction of the prolongation of the sleeping period caused by the CCl_4 liver cell damage in the groups treated as compared with the prolongation of the sleeping period of the CCl_4 control group (= 100%). The ED_{50} is determined by interpolation from the dose/effect curve.

Testing the antiulcerogenic action

The ulcer provocation is carried out on rats which have been made to fast for 24 hours (female, 180-200 g) by ligature of the pylorus (under ether narcosis) and the oral application of 100 mg/10ml/kg acetylsalicylic acid. The administration of the substances was carried out intraduodenally (2.5 ml/kg) immediately after the ligature of the pylorus. The closure of the wound was carried out by means of Michel clamps. 4 hours after this, the animals were destroyed whilst inebriated with ether by dislocation of the atlas and the stomach was resected. The stomach opened longitudinally is fixed on a cork board, and using a stereomicroscope with an enlargement of 10 X the number of size (= diameter) of any ulcers present were determined. The product of the degree of severity (according to the following scale of points) and the number of ulcers was used as the individual ulcer index.

Scale of points:

No ulcer	0
Diam. 0.1 – 1.4mm	1
1.5 – 2.4mm	2
2.5 – 3.4mm	3
3.5 – 4.4mm	4
4.5 – 5.4mm	5
> 5.5mm	6

As a measure of the antiulcerogenic effect one used the reduction in the mean ulcer index of each treated group as compared with that of the control group (= 100%).

Determination of the inhibition of the formation of glucose in the isolated prefused rat liver

For this purpose one uses young male Sprague-Dawley rats (160 to 200 g). The rats are kept in cages of up to 5 animals in a temperature-controlled room (23°C) with a fixed day/night rhythm (12/12 hours).

Food is withheld from the animals 20 to 22 hours prior to the operation. They are allowed to take water ad lib. The operation and the perfusion of the liver are carried out using the technique of R. Scholz et al. (Eur. J. Biochem. 38 (1973) 64-72). The perfusion liquid used is Kreb-Henseleit bicarbonate buffer (pH 7.4), which is saturated with an oxygen/carbon dioxide mixture (95/5) and contains 1.6 mmol/litre of L-lactate and 0.2 mmol/litre pyruvate. The perfusion liquid is pumped into the liver via a cannula inserted into the portal vein. The effluent perfusion liquid is collected via a cannula inserted into the Vena cava. The liver is perfused for approximately 2 hours. The test compounds are infused for 16 minutes each from the 32nd to the 80th minute after the perfusion in increasing concentrations (0.02 to 1.00 mmol/litre).

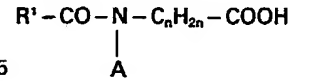
Samples of the effluent perfusion liquid are collected at one-minute intervals and analysed for glucose, lactate and pyruvate using standard enzymatic methods. The percentages shown in Table V relate to the condition occuring before and after the after the administration of the compounds, the changes caused solely by lactate and pyruvate being set as being equal to 100%.

Determination of toxicity

The toxicity investigations are carried out on female NMRI mice (body weight 22-26 g). The animals (5 animals per dose) are given food and water ad lib. Different doses of the substances are administered intraperitoneally. The duration of observation is 14 days. The LD_{50}, i.e. the dose at which 50% of the animals die, is determined graphically from the dose/effect curve.

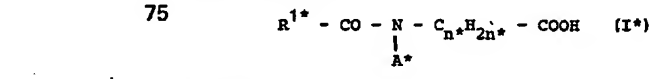
CLAIMS

1. Acylbiphenylylaminoalkanoic acids of the general formula I

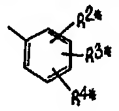


in which
R^1 signifies an aliphatic or alicyclic hydrocarbon radical or an optionally substituted phenyl group,
A signifies an optionally substituted and/or hydrogenated biphenyl radical,
N signifies a positive whole number from 3 to 5, and their salts of inorganic or organic bases.

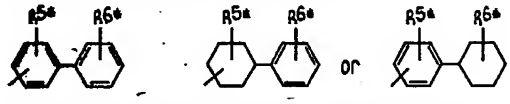
2. Acylbiphenylylaminoalkanoic acids of the general formula I*



in which
R^{1*} signifies an aliphatic hydrocarbon radical with 1 to 7 carbon atoms, an alicyclic hydrocarbon radical with 3 to 10 carbon atoms or a phenyl radical



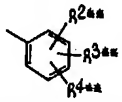
A^* signifies a group of the formula



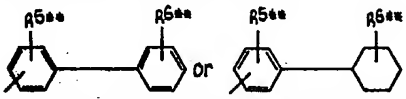
n^* signifies a positive whole number from 3 to 5,
R^{2*}, R^{3*} and R^{4*} are the same or different and signify a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group with 1 to 4 carbon atoms, an alkoxy group with 1 to 4 carbon atoms, an alkanoyloxy group with 2 to 5 carbon atoms, a nitro group or a trifluoromethyl group,
R^{5*} and R^{6*} are the same or different and signify a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a hydroxy group or a nitro group,and their salts of inorganic or organic bases.

3. Acylbiphenylylaminoalkanoic acids of the general formula I**

in which
R^1 signifies an aliphatic hydrocarbon radical with 1 to 5 carbon atoms, an alicyclic hydrocarbon radical with 5 to 7 carbon atoms or a phenyl radical



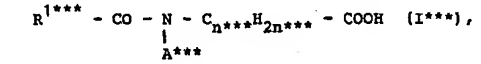
A^{**} signifies a group of the formula



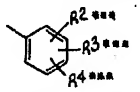
N^{**} signifies a positive whole number from 3 to 5,
R^{2**} signifies a hydrogen atom,
R^{3**} and R^{4**} are the same or different and signify a hydrogen atom, a halogen atom, a hydroxy group, a methoxy group, a methyl group, an alkanoyloxy group with 2 to 5 carbon atoms, a nitro group or a trifluoromethyl group,
one of the substituents R^{5**} or R^{6**} signifies a hydrogen atom and the other signifies a hydrogen atom, a halogen atom, a methyl group, a methoxy group, a

hydroxy group or a nitro group,
and their salts of inorganic or organic bases.

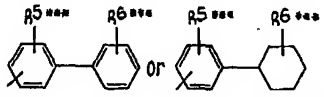
4. Acylbiphenylylaminoalkanoic acids of the general formula I***



in which
R^{1***} signifies an aliphatic hydrocarbon radical with 1 to 3 carbon atoms or a phenyl radical

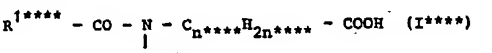


A*** signifies a group of the formula

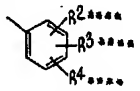


N^{***} is a positive whole number from 3 to 5,
R^{2***} signifies a hydrogen atom,
R^{3***} and R^{4***} are the same or different and signify a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxy group, a methoxy group or a trifluoromethyl group,
one of the substituents R^{5***} or R^{6***} signifies a hydrogen atom and the other signifies a hydrogen atom or a methoxy group,
and their salts of inorganic or organic bases.

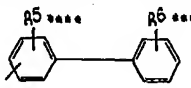
5. Acylbiphenylylaminoalkanoic acids of the general formula I****



in which
R^{1****} signifies an alkyl group with 1 to 3 carbon atoms, an alkenyl radical with 2 or 3 carbon atoms, or a phenyl group



A**** signifies a group of the formula



n^{****} signifies a positive whole number from 3 to 5,
R^{2****} signifies a hydrogen atom,
R^{3****} signifies a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxy group, a methoxy group or a trifluoromethyl group,
R^{4****} signifies a hydrogen atom or a chlorine atom,
one of the substituents R^{5****} or R^{6****} signifies a hydrogen atom and the other signifies a hydrogen atom or a methoxy group,
and their pharmacologically compatible salts of inorganic or organic bases.

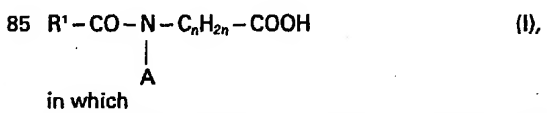
6. Compounds in accordance with Claim 4 or 5, in which A*** or A**** has the meaning of a 2-biphenylyl radical, and their pharmacologically compatible salts or inorganic or organic bases.

7. Compounds in accordance with Claim 5, in which R^{3****} signifies a fluorine atom, a chlorine atom, a hydroxy group or a methoxy group and R^5 and R^{6****} denote hydrogen atoms, and their pharmacologically compatible salts of inorganic or organic bases.

8. Compounds in accordance with Claim 5, in which A**** has the meaning of a 2-biphenylyl radical, R^{3****} signifies a fluorine atom, a chlorine atom, a hydroxy group or a methoxy group and R^{5****} and R^{6****} denote hydrogen atoms, and their pharmacologically compatible salts of inorganic or organic bases.

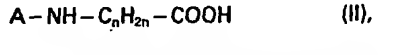
9. Pharmaceutical products containing as active ingredient one or more compounds in accordance with Claim 1 to 8.

10. Process for the production of acylbiphenylylaminoalkanoic acids of the general formula I

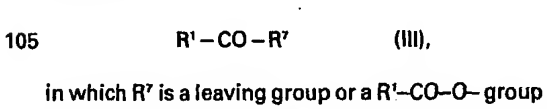


in which
R^1 signifies an aliphatic or alicyclic hydrocarbon radical or an optionally substituted phenyl group,
A signifies an optionally substituted and/or hydrogenated biphenyl radical,
n signifies a positive whole number from 3 to 5, and their salts of inorganic bases, characterized by the fact that
a) a biphenylylaminoalkanoic acid of the general formula II

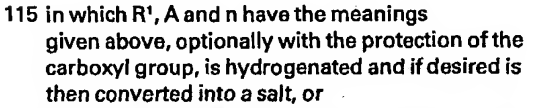
in which A and n have the meanings given above, optionally with the protection of the carboxyl group, is acylated with an acyl derivative of the general formula III



in which R^7 is a leaving group or a R^1–CO–O– group and R^1 has the meaning given above, and if desired is then converted into a salt or



in which R^1, A and n have the meanings given above, optionally with the protection of the carboxyl group, is hydrogenated and if desired is then converted into a salt, or
c) a functional acylbiphenylylaminoalkanoic acid derivative of the general formula V



in which R^1, A and n have the meanings given above and G signifies a functional derivative of a carboxyl group, is solvolysed and if desired is then converted into a salt.

11. A process for the production of acyl-

biphenylylaminoalkanoic acids of the general formula I according to to Claim 1, substantially as described with reference to the specific examples hereinbefore set forth.

12. Pharmaceutical compositions containing from 1% to 95% by weight of the total mixture of at least one compound according to Claim 1 to 8 in admixture with one or more solid or liquid pharmaceutically acceptable inert carriers.

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ANSWER 21 OF 44 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1980:447197 CAPLUS
DOCUMENT NUMBER: 93:47197
TITLE: Substituted amino acids
INVENTOR(S): Krastinat, Walter; Riedel, Richard; Wolf, Horst
PATENT ASSIGNEE(S): Byk-Gulden Lomberg Chemische Fabrik G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 65 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
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DE 2923731	A1	19800103	DE 1979-2923731	19790612
BE 876933	A1	19791212	BE 1979-46861	19790612
DK 7902449	A	19791215	DK 1979-2449	19790612
AU 7947978	A1	19791220	AU 1979-47978	19790612
AU 525423	B2	19821104		
JP 54163558	A2	19791226	JP 1979-73150	19790612
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EP 6218	B1	19820526		
R: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
GB 2024813	A	19800116	GB 1979-20409	19790612
FR 2432501	A1	19800229	FR 1979-14946	19790612
ES 481492	A1	19800301	ES 1979-481492	19790612
AT 1093	E	19820615	AT 1979-101912	19790612
ZA 7902943	A	19800625	ZA 1979-2943	19790613
CA 1153387	A1	19830906	CA 1979-329666	19790613

PRIORITY APPLN. INFO.: CH 1978-6504 19780614
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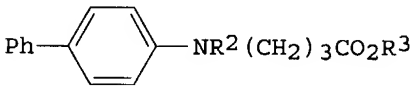


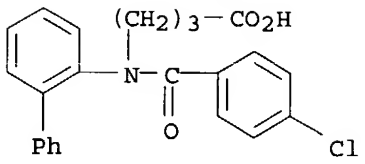
II

AB RCONR1CnH2nCO2H [I; R = aliphatic or alicyclic hydrocarbon residue, (un)substituted Ph; R1 = (un)substituted and/or hydrogenated biphenylyl; n = 3-5] were prepared as pharmacol.-active agents (e.g., ulcer inhibitors or antihepatotoxic agents). Thus, Br(CH2)3CO2Et was treated with 2-aminobiphenyl in the presence of EtN(CHMe2)2 for 3 h at 150° to give 63.7% γ-aminobutyrate II (R2 = H, R3 = Et), which was acylated with p-ClC6H4COCl at room temperature to give 75.6% II (R2 = p-ClC6H4CO, R3 = Et), which was saponified to give 72.1% II (R2 = p-ClC6H4CO, R3 = H). Data are given for the ulcer-inhibiting and antihepatotoxic activities of I in rats as well as the effects of I on gall and pancreatic secretions in rats.

IT **74296-86-9P 74296-88-1P 74296-90-5P**
74296-91-6P 74296-93-8P 74296-95-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and pharmacol. activity of)

RN 74296-86-9 CAPLUS

CN Butanoic acid, 4-[[1,1'-biphenyl]-2-yl(4-chlorobenzoyl)amino]- (9CI) (CA INDEX NAME)



RN 74296-88-1 CAPLUS
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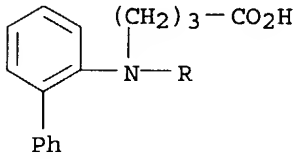

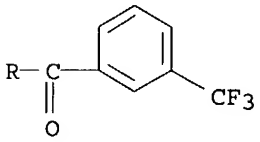

RN 74296-90-5 CAPLUS
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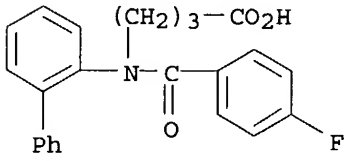

RN 74296-91-6 CAPLUS
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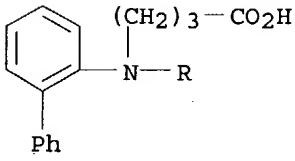

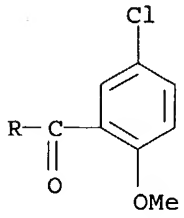

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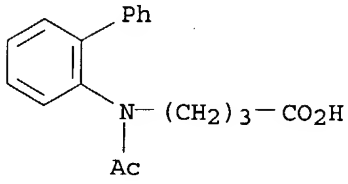

RN 74296-95-0 CAPLUS
CN Butanoic acid, 4-[[1,1'-biphenyl]-2-yl(1-oxo-2-butenyl)amino]- (9CI) (CA INDEX NAME)